TRS
TOXICOLOGY/REGULATORY SERVICES

December 7, 1998 Via UPS

Ms. Stephanie Mason
Division of OTC Products
Office of Drug Evaluation V
Center for Drug Evaluation and Research
Food & Drug Administration
5600 Fishers Lane, HFD-560
Rockville, MD 20857

Re: Benzethonium Chloride (BZC)

Dear Ms. Mason:

On behalf of Lonza Inc., we are submitting an outline for a proposed pharmacokinetic study to be conducted with benzethonium chloride (BZC). The purpose of providing this outline is to allow for Agency review and comment on the basic study design prior to developing a definitive protocol.

The other studies that were proposed, i.e. *in vitro* skin penetration studies in which aqueous and ethanol formulations will be evaluated using human and rat skin sections, will be standard studies for which definitive protocols will be developed and submitted for Agency review once agreement is reached on the design for the pharmacokinetic study.

We look forward to hearing from the Agency after review of the enclosed outline is completed.

Sincerely,

Gerald P. Schoenig

Gerald P. Schoenig, Ph.D.
Toxicology Consultant to Lonza Inc.

GPS/smg

Enclosure

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2345 HUNTERS WAY #3, CHARLOTTESVILLE, VIRGINIA 22911 ▪ TELEPHONE: 804-977-5957 ▪ FACSIMILE: 804-977-0899
Email: trs@trs.ova.net ▪ Website: www.trs.ova.net

Outline for a Study to Examine the Pharmacokinetics of Benzethonium Chloride in Rats Following Dermal Application as a Water-Based Formulation

Purpose

The purpose of this study will be to examine the pattern of appearance and disappearance of radioactivity in the blood and in the excreta of rats following dermal administration of ^{14}C-benzethonium chloride as a water-based formulation. Variables against which these parameters will be evaluated will include dose level and duration of treatment.

Study Design

Treatment Groups and Dose Levels

- Two groups of rats, each consisting of five males and five females, will be utilized in the study.
- The rats will be of the same strain and approximately the same age as those used in the NTP subchronic toxicity studies conducted on BZC.
- Rats in one group will be administered a "high" dose of BZC. Rats in a second group will be administered a "low" dose of BZC. The high dose will be the highest dose that can be administered dermally and will be defined within the constraints imposed by skin irritation and body surface area. The low dose will be approximately 1/10 of the high dose unless, a greater fraction of the high dose is necessary in order to administer enough radioactivity for analytical purposes.
- Prior to the initiation of the definitive study, two preliminary studies will be undertaken. The purpose of one preliminary study will be to define the maximum concentration of BZC in the form of a water based formulation that can be applied dermally once per day five days per week without producing more than slight dermal irritation. The purpose of the second preliminary study will be to determine time intervals for blood sampling in the definitive study so that the appearance and disappearance of ^{14}C-BZC equivalents can be tracked appropriately.

Test Article and Method of Application

- ^{14}C-radiolabeled BZC will be prepared and administered dermally in the form of a water-based formulation.
- The ^{14}C label will be placed on the N-methyl position in the BZC molecule. This site was selected for two reasons. First, it is a very stable portion of the molecule. Second, it is associated with the site of biological activity in the BZC molecule. Therefore, the radioactivity observed in the blood and excretion will represent all potentially active portions of the BZC molecule.
- The application site will be the shaved back.
- Following a 24-hour exposure period the skin at the application sites will be washed with soap and water to remove residual radioactivity.

Sample Collection Following a Single Application

- Blood samples (0.1 ml/sample) will be collected during the first 24 to 48 hours following the initial application for the purpose of defining the pattern of radioactivity in the blood following a single dermal application of BZC.
- Sampling intervals (six to eight) will be determined in a separate preliminary blood level study designed to define the time course of ^{14}C-BZC appearance and disappearance in the blood following a single dermal application of ^{14}C-BZC.
- For three to seven days following the initial application of ^{14}C-BZC, all excreta (urine and feces) will be collected for the purpose of defining the absorption and excretion rates and patterns for ^{14}C-BZC following a single dermal application.
- Urine and fecal samples will be collected separately over the following time intervals (hr.): 0 to 4, 4 to 8, 8 to 12, 12 to 24, 24 to 48, 48 to 72, etc.

Evaluation of Pharmacokinetic Parameters Following a Repeated Dose Regimen

- After the level of radioactivity recovered in the urine and feces decreases to an insignificant level, rats in both groups will receive additional dermal applications of BZC in the form of a water-based formulation at the high- and low-dose levels for a

period of 14 days. During the first 13 days, cold BZC will be applied. On the 14th day a second dose of ^{14}C-BZC will be applied.

- Following a 24-hour exposure, residual ^{14}C-BZC will be removed with soap and water, but daily applications of cold BZC will continue for an additional three to seven days.
- During the first 24 to 48 hours following the second application of the ^{14}C-BZC, blood samples will be collected for the purpose of defining the pattern of radioactivity in the blood following repeated dermal application of BZC. The same sampling intervals used in the single dose phase of the study will be utilized.
- For three to seven days following the second application of ^{14}C-BZC, all excreta (urine and feces) will be collected for the purpose of defining the absorption and excretion rates and patterns for ^{14}C-BZC following repeated dermal applications.

Potential Additional Evaluations

- If (after taking in account minor differences that may occur due to biological variation and/or age) significant differences are observed in the blood level patterns and/or rates or patterns of absorption and excretion between the data collected following a single dose versus that collected following repeated doses, the rats in both groups will be administered cold BZC for an additional 13 days, followed by a third dose of ^{14}C-BZC. The same parameters evaluated following a single dose and 14 doses will be evaluated once again.

Evaluation and Interpretation of Data

- Blood level data will be expressed in terms of BZC equivalents. At least the following pharmacokinetic values will be generated from these data: C_{max}, T_{max}, $t_{½}$ for elimination and area under the blood level versus time curve.
- Urine and fecal data will be expressed in terms of percent of administered radioactivity over the individual intervals in which they are collected and over the total collection period.

- It is anticipated that the data collected in this study will fully characterize the blood level, absorption patterns and excretion patterns of radioactivity following single and repeated dermal doses of ^{14}C-BZC in the form of a water-based formulation at both a high and low dose.